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Cancer Incidence among Swedish Patients Exposed to Radioactive Thorotrast: A Forty-Year Follow-up Survey

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Thorotrast is an α-particle-emitting radiological contrast medium that caused chronic exposure to internal α-particle radiation when it was administered systemically. Cancer incidence in 432 Swedish patients exposed to Thorotrast was evaluated by computerized linkage of the cohort with the Swedish Cancer Register. Standardized incidence ratios (SIRs) were calculated as the ratio of observed cases in the cohort to expected cases in the general population. A total of 170 cancers occurring in 152 individuals were reported, whereas only 57 cases were expected. The SIR was significantly increased for cancer at all sites (3.0), with the largest excesses noted for primary liver and gallbladder cancer (SIR = 39.2). Other significantly elevated risks were observed for liver cancer not specified as primary, small intestine cancer, stomach cancer, leukemia, kidney cancer, CNS tumors, and pancreatic cancer. Among women, there was a significantly increased risk for lung cancer, based on a small number. Our results show that cumulative radiation exposure is directly related to carcinogenesis in the liver and gallbladder, which is consistent with earlier findings. In addition, there may be a relationship between radiation exposure and the development of other solid tumors. **© 2002 by Radiation Research Society**

INTRODUCTION

Thorotrast is a commercially prepared α-particle-emitting colloidal suspension of thorium dioxide that was used worldwide as a contrast medium for a variety of radiographic procedures, mainly for visualization of vascular structures. It was introduced into clinical practice in the late 1920s and was used until the early 1950s, when growing recognition of its potential toxicity resulted in its withdrawal from the market. After intravascular injection, Thorotrast was retained in the body for life, mainly in the reticuloendothelial cells of the liver, spleen and bone marrow (*1, 2*). Hence these organs were continuously exposed to low-dose α-particle, β-particle, and γ radiation from ^{232}Th and its progeny. Alpha-particle radiation constitutes the most common exposure from ionizing radiation to humans. It is associated with increased mortality and cancer incidence, which has been shown in surveys of exposed populations in Denmark (*3*), Germany (*4*), and Japan (*5*).

The Swedish Thorotrast cohort was recently re-established, with follow-up extended through December 31, 1993. Mortality of the cohort was compared with that of the general population in Sweden (*6*). Important findings included significant, lifelong excesses in mortality from all causes, increasing with time to reach threefold 30 and 40 years after Thorotrast injection. There were significant dose–response relationships for all causes of death and for malignant tumors, consistent with an effect of cumulative radiation exposure on cancer development. The present paper focuses on site-specific cancer risks in relation to the administered amount of Thorotrast, age, sex and latent period.

PATIENTS AND METHODS

Data on the Swedish cohort of Thorotrast-exposed patients have been described in detail elsewhere (*6*). Briefly, 1,117 patients (63% males and 37% females) who received Thorotrast during cerebral angiography between 1932 and 1948 were identified by reviewing medical records and rosters from the Serafimer Hospital in Stockholm, the only operational neurosurgical department in the country at that time. Subjects were admitted to angiography because of neurological symptoms suggestive of serious underlying conditions.

After 361 individuals who died within 1 year after examination and 63 people lost to follow-up were excluded, 693 were left in the study. Of those, 261 died prior to January 1, 1958, leaving 432 individuals (56% males and 44% females). Survival through this date was required to enable computerized linkage of the cohort with the Swedish Cancer Register (SCR), which was established in 1958 and contains nationwide information on newly diagnosed cancers. Reporting to the register is mandatory for clinicians as well as for pathologists and cytologists. More than 96% of all cancers and cases of leukemia are reported to the register, most of them from at least two different sources (*7*).

Computerized linkage with the SCR for the period 1958–1993 was accomplished by means of the 10-digit personal identification number assigned to all Swedish citizens, beginning in 1947. This number consists of six digits based on year, month and day of birth, supplemented by a three-digit registration number and a check digit. Different cancer sites

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TABLE 1
Observed Number of Cancers by Site (ICD-7), Standardized Incidence Ratio (SIR), and 95% Confidence Interval (CI) among Male and Female Patients Exposed to Thorotrast

	Males			Females			Total		
Cancer site	Observed	SIR	95% CI	Observed	SIR	95% CI	Observed	SIR	95% CI
Stomach	5	12.2	3.9–28.5	1	6.2	0.1–35.0	6	10.5	3.9–23.0
Small intestine	2	14.3	1.4–51.4	1	9.1	0.2–50.9	3	12.0	2.4–35.2
Colon	1	0.5	0.0–2.5	6	2.8	1.0–6.1	7	1.8	0.8–3.6
Rectum	1	0.6	0.0–3.5	3	2.9	0.6–8.4	4	1.5	0.4–3.9
Liver, gallbladder	36	46.1	32.3–64.0	29	33.0	22.0–46.0	65	39.2	30.2–49.9
Liver, not primary	3	27.3	5.4–80.0	3	33.3	6.7–97.8	6	30.0	11.0–65.5
Pancreas	4	3.4	0.9–8.7	2	2.3	0.2–8.3	6	2.9	1.1–6.4
Lung, pleura, trachea, bronchi	3	0.9	0.2–2.7	4	4.6	1.2–11.6	7	1.7	0.7–3.5
Corpus uteri, unspecified				4	2.2	0.6–6.5	4	2.2	0.6–6.5
Ovary				2	1.2	0.1–4.3	2	1.2	0.1–4.3
Prostate	9	1.4	0.6–2.7				9	1.4	0.6–2.7
Kidney	5	4.0	1.3–9.3	2	2.5	0.2–9.1	7	3.4	1.4–7.0
Bladder	2	1.1	0.1–11.6	1	1.6	0.0–9.0	3	1.2	0.2–3.5
Other skin	1	0.9	0.0–5.1	2	3.7	0.4–13.3	3	1.8	0.4–5.4
Brain, CNS	3	3.8	0.8–11.3	2	2.5	0.3–9.0	5	3.1	1.0–7.4
Thyroid gland	0			2	6.9	0.8–16.4	2	4.6	0.6–16.4
Connective tissue	2	10.0	1.2–36.0	1	6.2	0.2–35.0	3	8.3	1.7–24.4
Sarcoma	2	3.0	0.4–10.8	0			2	1.7	0.2–6.0
Leukemia	8	7.1	2.9–14.7	3	4.5	0.9–13.1	11	6.1	2.9–11.2
All sites[a]	91	3.0	2.5–3.8	79	3.4	2.7–4.2	170	3.0	2.8–3.7

[a] Including cancer sites with <2 observed cases.

were classified and coded according to the International Classification of Diseases (ICD). Translations for 37 main cancer sites were undertaken, using the ICD-7 code system employed before 1975 (Table 1) (*8*).

The amount of Thorotrast injected was considered to be a surrogate measure of the radiation dose. Based on the injected volume of Thorotrast, six categories were defined for the analysis: <10 ml, 10–19 ml, >19 ml, unilaterally injected, bilaterally injected, and missing values. For 237 (55%) of the 432 patients in the study, information on the amount administered was found in the medical records and files. Among these patients, the mean injected volume was 15.5 ml (range 3–52 ml), and the average number of injections was 1.9. For the 195 individuals without information in the medical records, data on the number of injections were used for estimating the injected volume. For 9 patients, no details concerning the amount of Thorotrast administered were available.

Patients were followed from January 1, 1958, until death, emigration or December 31, 1993, whichever occurred first. The calculation of person-years was performed using the PYRS Program (*9*). The expected number of cancer cases was estimated by multiplying attained age-, sex- and calendar year-specific cancer incidence rates for the Swedish population by the corresponding number of person-years at risk. Attained age was classified into 18 groups, i.e. 0–4, 5–9,. . . , 80–84, and >85 years of age, and calendar years into categories 1958–1963, 1964–1969, 1970–1975, 1976–1981, and 1982–1993. Standardized incidence ratios (SIRs) were calculated as the ratios of observed to expected cases, with the observed numbers assumed to follow a Poisson distribution. Tests for trends by age at injection, time since injection, and injected volume of Thorotrast were computed using likelihood-based methods (*10*). To analyze the effect of injected volume of Thorotrast, time since injection, age at exposure, and gender, multivariate analyses were performed using Cox regression methods (*11*).

RESULTS

Among the 432 patients alive January 1, 1958, the mean year of birth was 1906 (range 1876–1939). The mean age at Thorotrast injection was 34 years for both men and women, with 13% examined before 20 years of age, 54% between 20 and 39 years, and 33% after 40 years of age. Most patients (44%) were injected between 1937 and 1941. Patients survived a median of 34 years, with longer survival for females (37 years) than males (32 years). The average age at death was 68 years (range 21–96), with 35 patients alive at the end of follow-up. The total number of years at risk was 7,284 (3,701 for males and 3,583 for females). The mean total amount of Thorotrast injected was 16.1 ml (range 3–52 ml), with no relationship between age at injection and amount of Thorotrast injected. Females received slightly smaller amounts than males (15.7 ml compared to 16.4 ml). Individuals with longer survivals received smaller than average amounts (11.1 ml for patients still alive at the end of follow-up). According to information taken from the original rosters, few of the individuals were injected extravascularly (13/432). Patients who lived more than 1 year after injection but were excluded because they died before 1958 were older at the time of injection (mean age 41 years), but they did not differ in any other aspect.

In total, 170 cancers (91 in males and 79 in females) occurring in 152 individuals were reported to the Swedish Cancer Register, whereas only 57 cases were expected in the general population. All of the cancers were verified histologically. Two cancers were registered for 16 subjects and three for one subject. The standardized incidence ratio (SIR) was significantly increased for cancer at all sites (SIR = 3.0), with virtually identical excesses in men (SIR = 3.0) and women (SIR = 3.4; Table 1). The highest increase was noted for primary liver and gallbladder cancer (SIR = 39.2), with 65 cases reported. In this category, women had

a lower risk than men (SIR = 33.0 and 46.1, respectively). The risk remained high, with a significant increase with time since exposure for both sexes (Fig. 1a). For those followed for >45 years, the SIR for liver and gallbladder cancer reached 51.1 (63.2 for males; 42.3 for females). The indications for injection (most commonly headache, epileptic seizures or paralysis) showed no gender-related differences.

The SIR for liver and gallbladder cancer was significantly related to age at exposure (Fig. 1b). Among subjects injected at less than 26 years of age, 21% of the patients developed a malignancy of the liver (25 cases), 16% of the patients injected at 26–45 years developed cancer (35 cases), and for those injected at >45 years, 11% developed a cancer (5 cases). Absolute rates calculated within the cohort gave a total of 92 liver cancers per 10,000 person years (PY) under risk for those 0–25 years of age at injection and 91/10,000 PY and 64/10,000 PY for those aged 26–45 years and >45 years at injection, respectively. These figures reflect the profound influence of the expected number of cases in relative risk calculations. A significant dose–response relationship was found, with increasing SIRs for liver and gall bladder cancer with larger amounts of Thorotrast administered, reaching 100 for those injected with more than 20 ml (Fig. 1c). The multivariate regression analysis showed that an increasing volume of injected Thorotrast was associated with the greatest risk for developing a liver tumor (relative hazard 2.40; $P < 0.001$), followed by decreasing age at injection (relative hazard 1.54; $P = 0.002$). No statistically significant difference in risk was seen between men and women.

Significantly elevated risks were observed for cancers of the small intestine (SIR = 12.0, $n = 3$), stomach (SIR = 10.5; $n = 6$), kidney (SIR = 3.4; $n = 7$), brain and CNS (SIR = 3.1, $n = 5$), and pancreas (SIR = 2.9; $n = 6$, Table 1). The overall risk for lung cancer was also increased (SIR = 1.7, $n = 7$), but the increase was significant only among females (SIR = 4.6, $n = 4$). The risk for breast cancer was slightly elevated (SIR = 1.3; $n = 8$). Significantly elevated risks, based on small numbers, were also noted for liver cancer not specified as primary (SIR = 30.0), which could represent misclassified metastases.

When non-chronic lymphatic leukemia was analyzed as a group, there was an overall significant sixfold increase (Table 1). A nonsignificant trend of increasing risk with increasing the amount of Thorotrast administered was seen, whereas the overall risk decreased with time since injection (Table 2). None of the patients with leukemia in the study cohort were injected before the age of 25 years (Table 2). When the same analyses were performed for all solid tumors except liver malignancies, the risks remained significantly increased for both sexes, with greater risks observed among women (Table 3). The trend of increasing SIR with larger amounts of injected Thorotrast was less compelling, although there was a significantly increased risk for those injected with >10 ml compared to those injected with <10

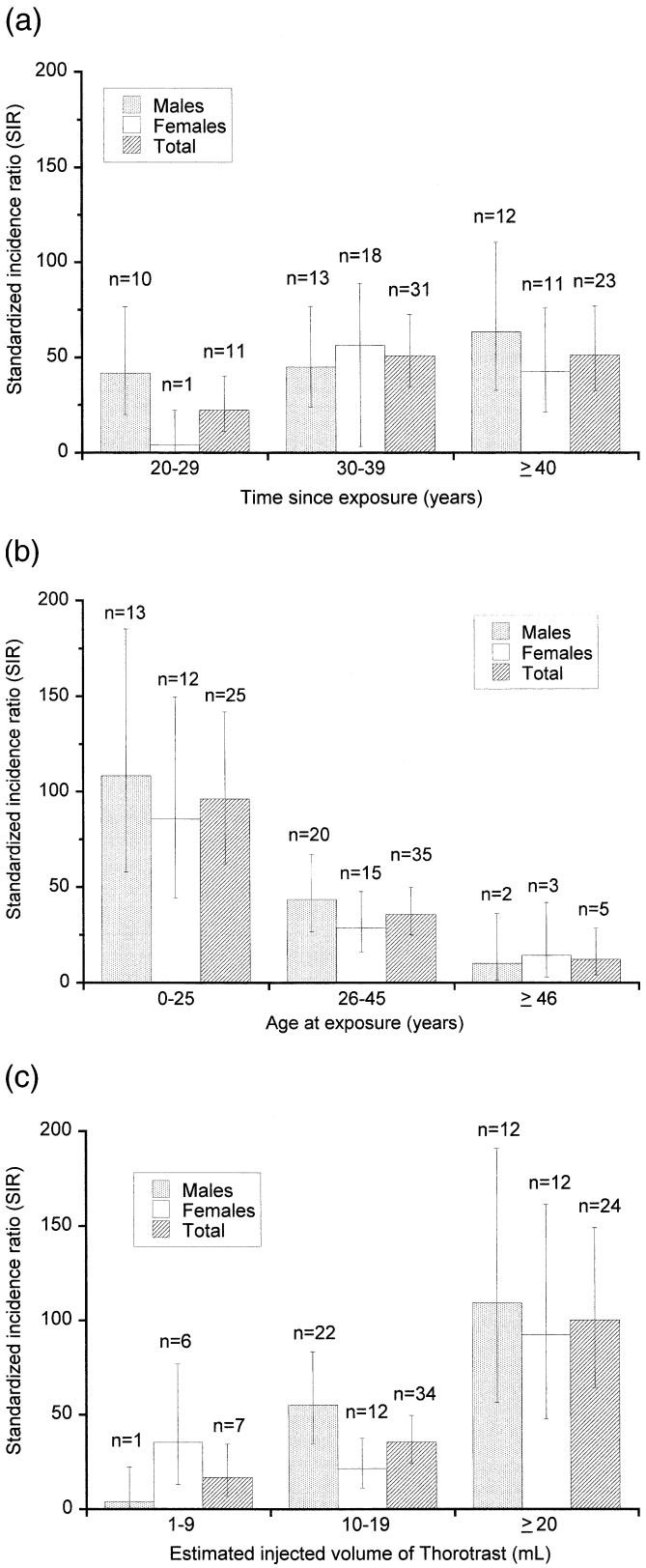

FIG. 1. Panel a. Risk of primary liver and gallbladder cancer in relation to time since exposure with 95% confidence intervals. Panel b. Risk of primary liver and gallbladder cancer in relation to age at exposure with 95% confidence intervals. Panel c. Risk of primary liver and gallbladder cancer in relation to amount of Thorotrast administered with 95% confidence intervals.

TABLE 2
Observed and Expected Number of Non-chronic Lymphatic Leukemia, Standardized Incidence Ratio (SIR), and 95% Confidence Interval (CI) among Male and Female Patients Exposed to Thorotrast

	Male				Female				Total			
	Observed	Expected	SIR	95% CI	Observed	Expected	SIR	95% CI	Observed	Expected	SIR	95% CI
Estimated injected volume, ml												
1–9	1	1.26	0.79	0.02–4.42	1	0.54	1.85	0.05–10.32	2	1.80	1.11	0.13–4.01
10–19	3	2.17	1.38	0.29–4.04	1	1.70	0.59	0.01–3.28	4	3.87	1.03	0.28–2.65
≥20	4	0.67	5.97	1.63–15.29	1	0.43	2.33	0.06–12.96	5	1.10	4.55	1.48–10.61
Time since injection, years												
20–29	2	1.71	1.17	0.21–6.18	2	1.04	1.92	0.23–6.95	4	2.75	4.45	0.40–3.72
30–39	5	1.15	4.35	1.41–10.15	1	0.82	1.22	0.03–6.79	6	1.97	3.05	1.12–6.63
≥40	1	0.56	1.79	0.05–9.95	0	0.51	0.00	0.00–7.23	1	1.07	0.93	0.02–5.21
Age at injection, years												
0–25	0	0.67	0.00	0.00–5.51	0	0.55	0.00	0.00–6.71	0	1.22	0.00	0.00–4.50
26–45	7	2.42	2.89	1.16–5.96	2	1.51	1.32	0.16–4.78	9	3.93	2.29	1.05–4.35
≥46	1	1.01	0.00	0.00–3.65	1	0.61	1.64	0.04–9.13	2	1.23	0.62	0.02–3.44

ml. The risk of solid tumors other than primary liver and gallbladder cancer increased significantly with time since injection and decreased with increasing age at injection (Table 3).

DISCUSSION

Awareness of the carcinogenic potential of ionizing radiation began early in the twentieth century (*12*), shortly after the discovery of X rays. The tumor-inducing effect is thought to be mediated either through a direct effect on the DNA molecule, or indirectly by the formation of free radicals in the cytosol (*13*). So far, epidemiological studies of human populations exposed to sparsely ionizing (low-LET) radiation form the main basis for quantifying the risk of radiation-induced cancer in humans. The detrimental effects of high-LET radiation have been estimated by establishing the relative biological effectiveness (RBE) for high-LET radiation compared to low-LET radiation, since only a few populations exposed to high-LET radiation exist. Individuals exposed to Thorotrast by angiography are unique in the sense that they were continuously irradiated by ^{232}Th and its α-particle-, β-particle- and γ-ray-emitting decay products.

The Swedish study cohort of 432 patients makes an important contribution, since follow-up is lifelong in most cases, enabling assessment of temporal trends in excess risks. The large percentage of women (44%) and the wide age range allow examination of gender- and age-related differences. By using the unique Swedish personal identification number and coding from the Swedish Cancer Register, valid comparison of the cohort with the general population is possible. Analyses based on cancer register data, as in our survey, ensure a high degree of accuracy with regard to the

TABLE 3
Observed Number of Solid Tumors,[a] Standardized Incidence Ratio (SIR), and 95% Confidence Interval (CI) among Male and Female Patients Exposed to Thorotrast

	Male			Female			Total		
	Observed	SIR	95% CI	Observed	SIR	95% CI	Observed	SIR	95% CI
Estimated injected volume, ml									
1–9	10	1.19	0.57–2.19	8	1.83	0.79–3.60	18	1.41	0.84–2.23
10–19	27	1.89	1.25–2.75	39	2.68	1.84–3.58	66	2.27	1.76–2.89
≥20	8	2.00	0.86–3.93	8	2.19	0.95–4.32	16	2.09	1.19–3.39
Time since injection, years									
0–19	1	0.33	0.01–1.83	4	1.82	050–4.66	5	0.90	0.29–2.10
20–29	10	1.14	0.55–2.10	11	1.41	0.71–2.53	21	1.27	0.79–1.94
30–39	15	1.75	0.84–2.23	20	2.71	1.66–4.19	35	2.20	1.53–3.06
≥40	19	3.00	1.81–4.99	20	3.61	2.21–5.58	39	3.29	2.34–4.49
Age at injection, years									
0–25	11	2.26	1.13–4.05	20	3.22	1.97–4.97	31	2.80	1.90–3.97
26–45	29	1.86	1.24–2.67	29	2.17	1.45–3.12	58	2.00	1.52–2.59
≥46	5	0.76	0.25–1.77	6	1.52	0.56–3.30	11	1.04	0.52–1.87

[a] Excluding primary liver cancer and liver cancer not specified as primary.

expected number of tumors, since the registers include a large number of cases. The precision of the Swedish Cancer Register is high (*7*), and although no reclassification was done, all tumors registered in the cohort were verified histologically. However, studying medically exposed individuals has a number of specific limitations. Patients are under heightened medical surveillance, and the disease under treatment may affect subsequent cancer risks. Therefore, selection bias can be expected to influence some of the results.

Important findings in our series include a lifelong excess in cancer incidence at all sites, with the greatest increase noted for primary liver and gallbladder cancer. Even when this site is excluded, the SIR remains significantly elevated for solid tumors as a group, as well as for liver cancer not specified as primary, and cancers of the small intestine, stomach, kidney, brain and CNS, pancreas, and female lung. Thorotrast conglomerates are deposited in all of these organs, although the amounts are small because of their low macrophage activity. The resulting dose rates are 5.3, 3.0, 2.8, 1.5, and 1.3 mGy/year for the lung, pancreas, small intestine, kidney, and stomach, respectively (*14*), compared to 0.22 Gy/year for the liver (*2*). In the Life Span Study of A-bomb survivors, a significant excess risk for all solid tumors combined was also demonstrated, with associations with radiation observed for cancers of the stomach, lung, and liver, but not for tumors of the pancreas and kidney (*15*). The five CNS tumors could have constituted the reason for examination if they had a low potential for malignancy. Misclassification could also explain some of the results. However, it is possible that the continuous exposure to radiation at low dose rates accounts for the increased risks observed for solid tumors that were not previously believed to be related to α-particle radiation.

Although the vast majority of Thorotrast-exposed patients have not been followed systematically, the number of neoplasms reported is substantial, and our results are in accordance with observations from other surveys of Thorotrast-exposed patients. In the Danish cohort of 999 exposed patients (*16*), the SIR for liver cancer was 126, with the cumulative incidence of cancer at all other sites reaching 86% 50 years after injection with Thorotrast. In Germany, the relative risk of liver cancer was 200, and excess rates among exposed patients compared to a control group were observed for several other cancer sites (gallbladder, non-chronic lymphatic leukemia, bone sarcoma, larynx carcinoma, pleural and peritoneal mesotheliomas), although incidence ratios were not calculated (*4, 17, 18*). The smaller Japanese study gave similar results (*19*), as did the Portuguese survey with follow-up ending in 1996 (*20*). The variations in point estimates could probably be explained by differences in the study populations and the comparison groups, as well as in the amounts of Thorotrast administered and the reason for the administration of Thorotrast.

The association between the risk for liver tumors and Thorotrast exposure was confirmed by the convincing relationships between the risk and the amount of Thorotrast injected and between the risk and the time since injection. In the Danish study (*3*), the SIR for liver cancer was also strongly related to time and injected volume, but it did not depend on the calculated dose rate. Dose–response and time associations have been established in the German survey as well, where a linear relationship was found between the dose rate and the tumor rate, but not between the mass of thorium dioxide injected and the tumor rate. Whether the dose rate, the cumulative dose, or the amount of Thorotrast injected has the largest effect on increased risk is not clear (*2, 21, 22*). Quantification of the doses by specific organs after Thorotrast administration is difficult, mainly because the distribution of thorium dioxide between and within the organs can vary by a factor of up to 100. In addition, thorium dioxide aggregates as conglomerates in which considerable self-absorption takes place, and there are indications that the liver/spleen deposition ratio is not constant (*2*). We chose to use injected volume as a surrogate dose measure. A similar approach was used by the Danish investigators, whereas whole-body counting and measurement of ^{220}Rn in breath were added for dosimetric calculations in the German survey. The use of the amount of Thorotrast injected as a surrogate dose measure facilitates comparison with other studies, and it is reasonable to believe that it reflects the dose rate. However, it should be emphasized that the amount of Thorotrast injected was recorded in medical records for only 55% of the exposed patients, adding further uncertainty to the dose estimates.

When all solid tumors except liver malignancies were analyzed as a group, the risk remained significantly increased for both sexes, with larger risks observed among women. In addition, there was a significant trend of increasing SIR with time since injection. In the Danish study, the risk for most solid tumors was also increased, but no relationship was observed between the SIR and the volume of Thorotrast injected or time since injection (*16*). The German and Japanese studies also demonstrated an increased risk for some solid tumors, but they could not establish any associations with dose or with time since injection (*18, 23*), possibly because of the relatively small number of cases. In the Life Span Study, on the other hand, the clear excess risk for all solid cancers was proportional to the background incidence rate and increased with attained age when adjusted for age at exposure (*15*). A twofold greater relative risk for females compared to males was also observed. The similar trends in our survey and the Life Span Study are interesting, although there are reasons to be careful in extrapolating the findings for the population of A-bomb survivors to other cohorts. Exposure to radiation from the explosions was brief and was approximately uniform throughout the body, and the radiation doses for the majority of the survivors were low. Most observations of carcinogenic effects have been made on populations exposed to high doses, and it is unclear how well these results can be extrapolated to low-dose radiation (*24*).

We found a significant trend of increasing relative cancer risk with younger age at injection of Thorotrast. This implies a higher susceptibility to ionizing radiation among the young, but it could also reflect the longer duration of exposure. The absolute risks in relation to age at injection did not differ to the same extent, which implies an effect of lower background rates on the relative risks. In the Life Span Study of A-bomb survivors, a similar relationship between relative risk and age at exposure was found for all solid tumors combined (*15*). However, with the exception of leukemia and cancer of the thyroid and breast, an additive, rather than multiplicative, risk model appeared to fit the data better (*25, 26*).

No consistent gender differences with regard to radiation-induced site-specific carcinogenesis have been established previously in exposed populations. In the Danish study, which had a sex distribution similar to ours, no gender-dependent difference in tumor rates was found. Interestingly, the German survey found excess risks for liver cancer among men similar to those in our study, with a male/female ratio of 1.6/1. This variance was ascribed to different baseline rates, but it could possibly be influenced by a higher prevalence among men for various risk factors such as hepatitis virus (*27*). It could also reflect gender differences in lifestyle, such as ethanol consumption. Taylor *et al.* (*28*) showed that giving dietary ethanol to beagles treated with americium increased the incidence of liver cancer by a factor of 2–3. It is known that cirrhosis accompanies many cases of liver cancer, but the exact mechanism for this interaction remains an active area of research (*29*). In the German study (*17*), about 30% of the patients with liver malignancies suffered from liver cirrhosis as well, compared to 10% among the exposed patients who did not develop liver cancer. A prior study of mortality in the Swedish cohort showed a significantly greater risk for mortality due to liver cirrhosis among women compared with men (standardized mortality ratio 22.8 compared to 8.3) (*6*). The smaller overall liver volume in women, resulting in a greater cumulative dose, might explain this finding. This hypothesis is somewhat contradictory to the finding of a lower risk for liver cancer among women, but it could represent a competing risk, since females who died from liver cirrhosis may not have reached the cumulative radiation dose necessary to develop a cancer.

Although the number of cases is small, we found a significantly increased risk for lung cancer among women who had received Thorotrast. As in most retrospective studies, detailed information on smoking habits was lacking, but taking into consideration that smoking was unusual among women at that time, this is an unlikely explanation for the increased risk. The lung tissue of patients injected intravenously with Thorotrast is exposed continuously through the exhalation of ^{220}Rn, ^{220}Rn and progeny dissolved in the blood and by Thorotrast conglomerates deposited in the lung parenchyma. The α-particle dose received by the radiation-sensitive basal cells might be expected to increase the lung cancer risk in exposed patients. However, no such excess has been established epidemiologically (*18*).

Different organs vary widely in susceptibility to the carcinogenic effects of ionizing radiation. Malignancies considered to be most readily caused by radiation include nonchronic lymphatic leukemia. We found a significant sixfold increase in this category, but there were too few cases ($n = 11$) to draw any conclusions regarding dose–response or time aspects. Since patients deceased before 1958 were excluded in the present analyses, it is possible that some of the hematological malignancies occurred among them. This needs to be assessed further by including mortality data from local parishes and medical records. Both the Danish (*3*) and the German (*18*) studies noted a 5–10-fold risk for leukemia, with induction times as long as 45 years, and both series failed to identify a relationship between leukemia risk and bone marrow dose in multivariate analysis.

The detrimental effects of Thorotrast have been shown convincingly through the lifelong follow-up of several exposed populations, and its consequences are still described in the literature (*30–33*). The substance had obvious radiographic advantages, but it may have been the most carcinogenic substance ever used for medical purposes. Additional research on individuals exposed to chronic α-particle radiation will assist in estimating the cancer risks as well as morbidity from other causes.

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